For females: QTc ≤ 450, 450 < QTc ≤ 470 and QTc > 470 msec.

Tabulations of the Max QTc change from trough QTc are also presented by treatment regimen and gender. Categories for these cross-tabulations are changes of < 30, 30 - 60, and > 60 msec.

PR Interval: The potential of the study regimens to affect the PR interval was also assessed by cross tabulations of the maximum PR (max PR) observed on either of the ECG recordings post dose versus the corresponding trough PR, presented by regimen and gender. Categories for these cross-tabulations were PR ≤ 200 and PR > 200 msec for both males and females.

Shifts in maximum QTc categories from trough to post-dose are presented by treatment and gender in the following table:

Cross-Tabulation of Trough QTc and Max Post-Dose QTc by Gender						
	Males: Observed (%)					
	EFV			ATV		
	n = 221			n = 225		
	Post-Dose Max QTc (msec)			Post-Dose Max QTc (msec)		
Trough QTc (msec)	≤ 430	430 - 450	> 450	≤ 430	430 - 450	> 450
≤ 430	192 (87)	13 (6)	1 (< 1)	196 (87)	15 (7)	2 (< 1)
> 430 - 450	6 (3)	4 (2)	2 (< 1)	6 (3)	4 (2)	2 (< 1)
> 450	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)
	Females: Observed (%)					
	EFV			ATV		
	(n = 103)			(n = 127)		
	Post-Dose Max QTc (msec)			Post-Dose Max QTc (msec)		
Trough QTc (msec)	≤ 450	450 - 470	> 470	≤ 450	450 - 470	> 470
≤ 450	98 (95)	2 (2)	0 (0)	120 (94)	6 (5)	0 (0)
> 450 - 470	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	0 (0)	0 (0)
> 470	0	0	0	0	0	0

The number of subjects experiencing a QTc prolongation (> 450 msec for males and > 470 msec for females) was small and comparable between treatment regimens (4 ATV; 7 EFV) with the majority of subjects being male. One male subject on EFV experienced a QTc interval > 500 msec.

The medication(s) taken concurrently were reviewed for subjects who had a measured QTc interval > 450 msec (males) and > 470 msec (females). With the exception of one subject on ATV and one subject on EFV, seven of the nine subjects were receiving drugs mentioned as possible contributors to QTc interval prolongation in the literature, specifically TMP/SMX, amitriptyline, and fluconazole. These agents are frequently co-

administered in this population and their affect on the QTc is difficult to assess in this substudy.

Tabulations of changes from trough QTc to post-dose maximum QTc are presented by treatment and gender in the following table:

Changes From Trough QTc to Post-Dose Maximum QTc by Gender						
	Males			Females		
	Observed/Evaluable (%)			Observed/Evaluable (%)		
	Change (msec)			Change (msec)		
Treatment	< 30	30 - 60	≥ 60	< 30	30 - 60	≥ 60
EFV (N = 324)	209/221 (95)	12/221 (5)	0/221 (0)	94/103 (91)	9/103 (9)	0/103 (0)
ATV (N = 352)	193/225 (86)	29/225 (13)	3/225 (1)	111/127 (87)	15/127 (12)	1/127 (< 1)

The change from trough QTc interval to post-dose maximum QTc interval was < 30 msec for the majority of subjects and was comparable between regimen and gender. More subjects in the atazanavir arm had change from trough QTc interval to post-dose maximum QTc interval from 30 – 60 msec. Four subjects (3 males and 1 female) on ATV had changes ≥ 60 msec from trough QTc to post-dose maximum QTc. No QTc interval for the these four subjects exceeded 470 msec, although the QTc interval for one male subject exceeded 450 msec.

PR Interval

At trough drug concentrations, the mean PR interval was 5 msec shorter for subjects receiving EFV compared with subjects receiving ATV. Minimal changes in the mean post-dose PR intervals from trough were observed on both treatment regimens. The summary statistics for the PR intervals are summarized in the following table:

Summary Statistics for PR Interval		
	Time	Mean (SE) [min, max] (msec)
Treatment	Post-Dose	
EFV (n =324)	0 hour	154 (1.2)
	2 - 3 hours	153 (1.1)
	6 - 12 hours	152 (1.1)
ATV (n = 352)	0 hour	159 (1.2)
	2 - 3 hours	160 (1.2)
	6 - 12 hours	159 (1.1)

Seven of 324 evaluable subjects (2.2%) treated with EFV and 16 of 352 evaluable subjects (4.5%) treated with ATV experienced first degree AV block (PR > 200 msec) on at least one ECG. No ECG diagnosis other than first degree AV block was reported.

Maximum PR intervals for atazanavir-treated subjects ranged from 265 msec to 307 msec.

RR Interval and Heart Rate

Small but statistically significant differences were noted in the heart rates of subjects receiving atazanavir versus efavirenz. The mean heart rate of atazanavir-treated subjects was 3 beats per minute lower than efavirenz-treated subjects. Small but statistically significant differences were also noted in the RR intervals between treatment regimens, consistent with the small difference noted in heart rate.

Blood Pressure of Atazanavir-Treated Subjects

Mean blood pressure of atazanavir-treated patients at baseline was 115/74 and mean blood pressure at 48 weeks of treatment was 114/73; this difference was not statistically significant. No significant difference in blood pressure of atazanavir versus efavirenz treated patients was observed at 48 weeks.

Discontinuations/Deaths Due to Cardiac Events

There were five deaths among randomized subjects in study 034 reported. All five were unrelated to cardiovascular causes. Two deaths occurred on the ATV regimen and three on the EFV regimen. All deaths were considered unrelated to study therapy. Three of the five deaths occurred after the discontinuation of study therapy. None of these cases were described as sudden death.

Amendment #2 to study 034 defined specific adverse events related to major cardiovascular toxicity that required drug discontinuation. These events were:

- QTc interval > 500 msec
- Heart rate < 40 bpm
- Pause length > 3 seconds on ECG
- Clinical symptoms potentially related to heart block
- Third degree (i.e., complete) heart block

No subjects discontinued due to these cardiovascular events. Discontinuations due to other cardiovascular events occurred in the EFV arm only and are summarized in the following table:

Cardiovascular Adverse Events Leading to Discontinuation Study 034

	ATV	EFV
	N = 404	N = 401
COSTART PREFERRED TERM		
Hypertension	0	1(<1)
Myocardial Infarction	0	1(<1)
Palpitation	0	1(<1)
Syncope	0	1(<1)
Vasodilatation	0	1(<1)

CV Events Considered to be Serious Adverse Events
Four CV events were assessed as SAEs by the investigators and all occurred in EFV treated patients; there were 2 events of syncope, 1 myocardial infarction, and 1 event of hypertension.

Cardiovascular Events of All Grades
Cardiovascular events of all grades were reported with roughly equal frequency on both treatment arms, although vasodilatation appeared to occur more frequently in EFV-treated patients. Review of adverse events potentially related to effects on the QT and PR interval were reviewed. Events, in general, were mild, self-limiting, or were due to non-cardiac related events (i.e. anemia).

Cardiovascular Events Occurring in Study 034 Grades 1-4		
	ATV	EFV
	N = 404	N = 401
COSTART PREFERRED TERM		
CARDIOVASCULAR SYSTEM	35(9)	46(11)
Vasodilatation	11(3)	27(7)
Hypertension	5(1)	3(< 1)
Palpitation	5(1)	7(2)
Syncope	5(1)	5(1)
Hypotension	2(< 1)	3(< 1)
AV Block First Degree	1(< 1)	0
Bradycardia	1(< 1)	0
Cardiomyopathy	1(< 1)	0
Extrasystoles Ventricular	1(< 1)	0
Feeling of Increased Heart Rate	1(< 1)	0
Hemorrhage	1(< 1)	3(< 1)
Tachycardia	1(< 1)	3(< 1)
Thrombosis	1(< 1)	0
Varicose Vein	1(< 1)	0
Anomaly Vascular	0	1(< 1)
Bundle Branch Block	0	1(< 1)
Disorder Cardiovascular	0	2(< 1)
Disorder Vascular	0	1(< 1)
Myocardial Infarction	0	1(< 1)
Phlebitis	0	1(< 1)

Cardiovascular events assessed by investigators as being related to study therapy appeared to be more common in EFV-treated subjects. This appeared to be due to the more frequent occurrence of vasodilatation in the EFV arm. A review of case narratives for the adverse events of palpitations and syncope did not reveal any clinically significant effect of atazanavir on the cardiovascular system.

Cardiovascular Adverse Events in Study 034 Assessed as Related to Study Therapy		
	ATV	EFV
	N=404	N=401
COSTART PREFERRED TERM		
CARDIOVASCULAR SYSTEM	13 (3)	30 (7)
Vasodilatation	6 (1)	21 (5)
Palpitation	4 (< 1)	3 (< 1)
Syncope	2 (< 1)	4 (< 1)
Hypertension	1 (< 1)	2 (< 1)
Disorder Cardiovascular	0	1 (< 1)
Hypotension	0	1 (< 1)
Tachycardia	0	2 (< 1)

Grade 3-4 cardiovascular events occurred in 3 atazanavir treated patients (1 event each of hypotension, syncope, and bradycardia). The 3 events occurring in atazavanir were related to one event of meningoencephalitis (bradycardia), and two events of grade 3-4 anemia (hypotension and syncope). Five grade 3-4 cardiovascular events occurred in efavirenz treated subjects (1 event each of syncope, palpitations, myocardial infarction, hypertension, and disorder cardiovascular).

Summary of Cardiovascular Assessment in Study 34
Cardiovascular events were reported in roughly equal numbers between subjects receiving atazanavir and efavirenz. Events potentially related to arrhythmia were reviewed; events, in general, were mild, self-limited, and attributable to causes other than arrhythmia.

24-Week Data – Study 043
Twelve-lead ECGs were obtained at baseline on day 1 (prior to study drug administration). Three 12-lead ECGs were to be performed on study weeks 2, 12, 24, and 48. The first ECG (pre-dose [trough]) was performed prior to taking study medications on that day, the second ECG was performed 2 - 3 hours post-dose, and the third ECG was performed 6 - 12 hours post-dose. The ECG analysis included data for 280 subjects who were treated in study 043 and for whom ECG measurements were collected and reviewed.

Three subjects (ATV, 1 subject; LPV/RTV, 2 subjects) had a QTc interval prolongation at baseline, and nine subjects (ATV, 2 subjects; LPV/RTV, 7 subjects) experienced a post-baseline QTc prolongation. The majority of subjects with prolonged QTc interval were male. No subjects experienced a post-baseline QTc interval prolongation > 500 msec.

The QTc interval change from baseline category was comparable between the treatment regimens and was < 30 msec for the majority of male and female subjects. Eleven

subjects experienced a QTc interval change from baseline > 60 msec (ATV, 2 subjects; LPV/RTV, 9 subjects); nine of these subjects were male.

QTc Interval Change From Baseline Categories Treated Subjects - Males				
		QTc Interval Change Categories (msec)		
			Treatment Regimen	
			ATV	LPV/RTV
Week	Time	Summary Statistics	N = 111	N = 119
B/L	Pre-dose	<30	105/105 (100)	113/113 (100)
		30-60	0/105 (0)	0/113 (0)
		>60	0/105 (0)	0/11 (0)
	Maximum On-study	<30	77/107 (72)	77/115 (67)
		30-60	28/107 (26)	31/115 (27)
		>60	2/107 (2)	7/115 (6)

QTc Interval Change From Baseline Categories Treated Subjects - Females				
		QTc Interval Change Categories (msec)		
			Treatment Regimen	
			ATV	LPV/RTV
Week	Time	Summary Statistics	N = 33	N = 27
B/L	Pre-dose	<30	31/31 (100)	25/25 (100)
		30-60	0/31 (0)	0/25 (0)
		>60	0/31 (0)	0/25 (0)
	Maximum On-study	<30	22/30 (73)	17/25 (68)
		30-60	8/30 (27)	6/25 (24)
		>60	0/30 (0)	2/25 (8)

PR Interval

Baseline measurements were comparable between the treatment regimens. Mean pre-dose (trough) PR intervals at weeks 2, 12, and 24 were comparable between treatment regimens. Minimal increases from baseline were observed in mean post-baseline PR intervals on both treatment regimens at all weeks and time points (maximum mean change observed: ATV, + 5 msec; LPV/RTV, + 3 msec). At weeks 12 and 24, the mean PR interval changed from the mean PR interval at pre-dose (trough) by -2 msec and +1 msec, respectively, on the ATV treatment regimen and by 0 msec and -2 msec, respectively, on the LPV/RTV treatment regimen.

Summary Statistics of PR Interval
Treated Subjects – Week 24

		Treatment Regimen	
		ATV	LPV/RTV
Time point	Summary Statistics[a]	N = 144	N = 146
Week 24			
Pre-dose (trough)	N	111	116
	Mean (SE)	156 (1.8)	158 (2.0)
	Median (min, max)	157	154
Maximum (Week 24)	N	111	117
	Mean (SE)	163 (1.7)	163 (2.0)
	Median (min, max)	163	160

The number of subjects experiencing post-baseline PR interval prolongation (> 200 msec) was comparable between the treatment regimens; however, the subjects on the LPV/RTV treatment regimen were more likely to have PR interval prolongation at multiple time points than subjects on the ATV treatment regimen. Eight of 139 subjects (6%) on the ATV treatment regimen and eight of 141 subjects (6%) on the LPV/RTV treatment regimen experienced first degree AV block (PR > 200 msec) on at least one post-baseline ECG. Most of these events occurred in male subjects.

Heart Rate

Mean heart rates of atazanavir-treated subjects were 1–5 bpm faster than LPV/RTV treated patients at all timepoints, including pretreatment baseline. Minimal changes from baseline in post-baseline recordings were observed on either treatment regimen.

Blood Pressure

Mean blood pressure at baseline and 24 weeks for atazanavir-treated patients was 117/75 and 117/76 respectively. These were similar to mean blood pressures observed for LPV/RTV treated patients.

Discontinuations/Deaths Due to Cardiac Events

There was one death reported on the ATV regimen that was considered unrelated to study therapy. No cardiovascular events led to discontinuation from study therapy.

CV Events Considered to be Serious Adverse Events
Two CV events were reported as SAEs. One atazanavir subject was assaulted with a knife; cause of death was listed as traumatic cardiac arrest. One LPV/RTV subject experienced a myocardial infarction on study.

Cardiovascular Events of All Grades
The following table summarizes all cardiovascular events reported during study 043:

Cardiovascular Events Occurring in Study 043 (Grades 1-4)		
	ATV	LOP/RTV
	N = 144	N = 146
COSTART PREFERRED TERM		
Cardiovascular System	8 (6)	8 (5)
Angine Pectoris	1 (<1)	0
Arrest Heart	1 (<1)	0
Arrhythmia	0	1 (<1)
Disorder Coronary Artery	0	1 (<1)
Extrasystoles	1 (<1)	0
Fibrillation Atrial	0	1 (<1)
Hemorrhage	1 (<1)	0
Hypertension	2 (1)	4(3)
Murmur Heart	0	1 (<1)
Myocardial Infarction	0	1 (<1)
Palpitation	0	1 (<1)
Syncope	0	1 (<1)
Tachycardia	1 (<1)	0
Vasodilation	2 (1)	2 (1)

No causality assessment by investigators was provided for cardiovascular events in this application.

Cardiovascular Assessment from Other Supporting Studies
As mentioned previously, ECG data was also collected from other trials submitted with this application. Phase 3 study 045 (antiretroviral-experienced subjects) was designed to evaluate ECG parameters by obtaining a baseline ECG measurement prior to study drug administration and by measuring serial ECG parameters (pre-dose, 2 -3 hours post-dose, and 6 - 12 hours post-dose) multiple times over the 48 week treatment period; limited data through 16 weeks has been provided for subjects enrolled in this study.

The rollover phase 2 studies 007/041 and 008/044 were amended to include ECG measurements. Three serial ECGs (pre-dose [trough], 2 -3 hours post-dose, and 6 - 12 hours post-dose) were collected.

The following table summarizes the on-study QT interval changes seen in these studies. In this table doses of ATV received in 041 are combined (200 mg, 400 mg, and 500 mg) and in 045 (ATV 300/RTV 100 and ATV 400/SQV 1200).

On-Study QTc Interval Changes From Trough - Phase 2/3 Studies						
	Number with any QTc Interval Change from Trough Number Assessed (%)					
	041		044		045	
QTc Interval (msec)	ATV Combined N=147	NFV N=47	ATV 400 N= 172	ATV 600 N= 127	ATV Combined N=228	LOP/RTV N=91
Males	**N=100**	**N=29**	**N=108**	**N=79**	**N= 171**	**N=87**
< 30	87/100 (87)	28/29 (97)	96/108 (89)	66/79 (84)	136/171 (80)	72/83 (87)
30 - 60	12/100 (12)	1/29 (3)	12/108 (11)	11/79 (14)	30/171 (18)	10/83 (12)
> 60	1/100 (1)	0/29 (0)	0/108 (0)	2/79 (3)	5/171 (3)	1/83 (1)
Females	**N=47**	**N=18**	**N=63**	**N=44**	**N=49**	**N=26**
< 30	42/47 (89)	17/18 (94)	55/63 (87)	41/44 (93)	38/47 (81)	23/26 (88)
30 - 60	5/47 (11)	1/18 (6)	8/63 (13)	3/44 (7)	9/47 (19)	3/26 (12)
> 60	0/47 (0)	0/18 (0)	0/63 (0)	0/44 (0)	0/47 (0)	0/26 (0)

In study 041, more subjects receiving atazanavir versus nelfinavir had QTc changes from trough between 30 and 60 mec, however, the number of nelfinavir subjects with evaluable ECG data is too small to reach any conclusions. More subjects receiving atazanavir versus LPV/RTV in study 045 had a QTc change from trough between 30 and 60 msec.

Overall Cardiac Safety Summary

The number of ATV-treated subjects experiencing an on-study QTc interval prolongation (> 450 msec for males and > 470 msec for females) was infrequent and comparable among treatment regimens. Overall, one EFV-treated subject, one nelfinavir-treated subject and no ATV-treated subjects reported a significantly prolonged QTc interval (> 500 msec). No adverse events potentially related to prolongation of the QT interval and arrythmia were identified. Pharmacokinetic evaluation of the potential effects of

atazanavir on the QT interval revealed no effect considered to be potentially clinically significant, although data from study 076 is limited by the lack of a positive control.

The ACC/AHA/NASPE 2002 Guidelines for Implantation of Cardiac Pacemakers and Antiarrythmic Devices recommend pacemaker placement for first degree AV block greater than 300 msec in patients with left ventricular dysfunction and symptoms of congestive heart failure; in these patients a shorter AV interval results in hemodynamic improvement. PR interval prolongations of this magnitude were uncommon in clinical trials of atazanavir 400 mg, with a PR interval greater than 300 msec being observed on one occasion in one subject.

PR intervals of this magnitude were observed on several occasions in healthy volunteer pharmacokinetic studies. In a drug-drug interaction study of atazanavir and diltiazem, one subject receiving 400 mg atazanavir concomitantly with 180 mg diltiazem was observed to have a PR interval greater than 300 msec; this was likely due to a combination of PR interval prolongation due to elevated levels of diltiazem and a relatively modest prolongation of the PR interval by atazanavir. Two healthy volunteers receiving 800 mg atazanavir were observed to have PR intervals greater than 300 msec.

In clinical trials, the number of subjects experiencing a post-dose PR interval prolongation (> 200 msec) was generally comparable among treatment regimens. PR intervals > 300 msec were observed very infrequently; only one subject receiving atazanavir in study 034 was observed to have a PR interval greater than 300 msec. Overall, across the five phase 2 and 3 studies, PR interval prolongations > 200 msec were seen in 53 of 911 subjects (5.8%) receiving the recommended 400 mg dose of ATV. This incidence was comparable to that seen for other protease inhibitors: 5.2% for subjects receiving LPV/RTV and 8.5% for subjects receiving NFV. The incidence was higher than seen for efavirenz-treated subjects in study 034 (2%).

Cardiac conduction abnormalities other than first degree AV block that were potentially attributable to atazanavir were also uncommon. In clinical trials, one subject who intentionally ingested about 29 gms of atazanavir developed a severely prolonged PR interval and bifascicular block that resolved five days following withdrawal of treatment. In study 034 bundle branch block was reported in one ATV subject and one EFV subject; neither of these events were reported as significant adverse events or resulted in discontinuation from study.

Another patient receiving atazanavir through the expanded access protocol was hospitalized with a junctional rhythm eleven days after starting ARV therapy with atazanavir (CYP 3A inhibitor), delavirdine (CYP 3A inhibitor), lamivudine and tenofovir, while concomitantly receiving verapamil (CYP3A substrate) for hypertension. The junctional rhythm was most likely due to markedly elevated levels of verapamil; the relative contribution of atazanavir to any conduction disturbances was likey minimal. However, this case does highlight the clinical importance of drug-drug interactions with the comcomitant use of CYP3A substrates, particularly calcium channel blockers.

In summary, while pharmacokinetic studies designed to evaluate effects of atazanavir revealed moderate dose dependent prolongation of the PR interval, clinical events were uncommon. Asymptomatic first degree AV block was the most common ECG abnormality observed. It is likely that this effect of atazanavir will impact predominantly those patients who develop high serum concentrations of atazanavir, particularly those with significant left ventricular dysfunction or other cardiac abnormalities.

7.4.4 **Special Safety Considerations – Diabetes**

Protease inhibitor labels currently carry the following class warning:

"New-onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established."

In order to evaluate the effect of atazanavir on glucose metabolism, the applicant collected data on fasting insulin, glucose and C-peptides in studies 034 and 043. No clinically meaningful differences between atazanavir and efavirenz-treated patients were observed over 48 weeks of therapy in treatment-naïve study 034. Mean fasting glucose and mean fasting insulin levels increased slightly over baseline in both groups. The incidence of grade 3-4 hyperglycemia was uncommon and comparable between groups (< 1%). New onset diabetes was reported in two atazanavir-treated patients and one efavirenz-treated patient.

In study 043 no clinically meaningful differences were observed between atazanavir and lopinavir/ritonavir-treated patients in mean changes in fasting glucose, insulin or C-peptide over 24 weeks of therapy. Any grade of hyperglycemia was observed in 11% of subjects in each treatment arm and grade 3-4 hyperglycemia was observed in one subject receiving atazanavir. The adverse event of hyperinsulinemia was reported in one subject receiving atazanavir.

In study 045 of highly treatment-experienced patients any grade of hyperglycemia was reported in 16% of subjects receiving ATV/RTV and LPV/RTV versus 8% of subjects receiving ATV/SQV over 16 weeks of therapy.

In summary, no meaningful differences in fasting glucose and insulin levels and in the incidence of new onset diabetes were observed between atazanavir and comparators in clinical trials.

7.4.5 General Safety Findings

Study AI424007 (007) – As mentioned previously, this study randomized 420 antiretroviral naïve HIV-infected subjects (98 in stage 1, 322 in stage 2) and was a two-stage, randomized, active-controlled, four arm study designed to evaluate and compare the safety, tolerability, and antiviral activity of 1) atazanavir at 3 different doses to NFV over 2 weeks of monotherapy; and 2) atazanavir at 3 different doses in combination with d4T and ddI versus NFV in combination with d4T and ddI over 46 additional weeks. Enrollment was restricted to antiretroviral naïve subjects who had a CD4 cell count of ≥100 cells/mm^3 (≥75 cells/mm^3 in subjects with no prior AIDS-defining diagnoses) and a plasma HIV RNA viral load > 2,000 copies/mL. The study was blinded to the dose of atazanavir.

Clinical adverse events were reported frequently with ≥ 90% of treated subjects in all treatment regimens reporting at least one adverse event of any grade. The rates of grade 3 - 4 adverse events in the atazanavir treatment regimens were generally comparable to NFV: atazanavir 200 mg (11%), 400 mg (26%), 500 mg (26%), NFV (20%).

The most frequently reported adverse events were infection (46% - 60%), diarrhea (23% - 61%), nausea (18% - 35%), abdominal pain (22% - 31%), headache (19% - 26%), peripheral neurologic symptoms (19% - 25%), vomiting (15% - 20%), and rash (12% - 22%). Diarrhea, a well-recognized side effect of nelfinavir, was reported by more subjects (61%) in the nelfinavir regimen compared to subjects (23% - 30%) in the atazanavir regimens ($p < 0.0001$). Jaundice and scleral icterus were reported only by subjects in the atazanavir regimens ($p < 0.03$ for all atazanavir regimens compared to NFV for jaundice). More nausea (35%) was reported in the atazanavir 400 mg regimen compared to NFV (17%) ($p < 0.01$). Rash was observed more frequently on atazanavir 400 mg and 500 mg (22% and 21%, respectively) than on atazanavir 200 mg (12%) and NFV (14%).

The overall incidence of pancreatitis was 3.4% and was comparable across treatment regimens. This was most likely due to the contribution of didanosine and stavudine nucleoside backbone.

Deaths

Six deaths were reported. One atazanavir 200 mg subject died from a gunshot wound 102 days after last the dose of study medication and one atazanavir 500 mg subject died of sepsis and lactic acidosis 50 days after last dose of study medication. Two other deaths, one in an atazanavir 500 mg subject and one in a NFV subject, were considered to be related to lactic acidosis. One atazanavir 200 mg subject died with immediate cause of death specified as liver failure (with complications of HIV disease), which was represented as hepato-renal syndrome as a consequence of multi-organ failure possibly due to Kaposi's Sarcoma. An additional atazanavir 500 mg subject was reported to have died of multifocal Kaposi's Sarcoma.

Serious Adverse Events

Serious adverse events were reported in 15-20% of atazanavir-treated patients and in 14% of nelfinavir-treated patients. SAEs were reported with roughly equal frequency between regimens. The majority of serious adverse events were judged to be unrelated to the protease inhibitor by the investigators. SAEs potentially related to atazanavir therapy included three events of hyperbilirubinemia, one event of icterus, one event of diabetes mellitis, one event of allergic reaction, and several events of hepatitis/liver enzyme abnormalities. Use of atazanavir, hyperbilirubinemia and the risk for hepatotoxicity are discussed elsewhere in this review.

Adverse Events Leading to Discontinuation of Study Therapy

Twenty-eight (7%) subjects discontinued due to one or more adverse events; the rate of discontinuation was comparable across treatment regimens. Overall, these 28 subjects reported 42 adverse events as reasons for discontinuation and 29 of these adverse events were considered at least possibly related to study drug. Two atazanavir subjects (one 200 mg and one 400 mg) discontinued due to lactic acidosis. In addition, three atazanavir (one 200 mg and two 500 mg) discontinued due to hyperbilirubinemia which was thought to be related to the drug. Two atazanavir (one 200 mg and one 400 mg) and one NFV subject discontinued as a result of lipodystrophy which was thought to be related to the study drug. Two atazanavir subjects (one 400 mg and one 500 mg) discontinued for rash. Discontinuations due to liver enzyme elevations are discussed in a separate section of this review.

Laboratory Abnormalities

With the exception of hyperbilirubinemia, laboratory adverse events were generally comparable across treatment regimens. Grade 1-4 hyperbilirubinemia was observed in 72-91% of atazanavir-treated subjects and grade 3-4 hyperbilirubinemia was observed in 20-47% of atazanavir-treated subjects. The hyperbilirubinemia was clearly dose dependent and predominantly indirect; this topic and other liver enzyme abnormalities are discussed at length under special safety considerations.

Fasting lipid profiles were available on approximately 50% of treated subjects. While atazanavir and nelfinavir treated subjects had similar lipid profiles at baseline, median lipid concentrations of total cholesterol, fasting LDL cholesterol and fasting triglycerides were approximately 20 mg/dL higher in the NFV regimen than in atazanavir regimens at week 48. Eighteen percent of NFV-treated subjects had LDL cholesterol $\geq$ 160 mg/dL at week 48, compared to at most 6% in atazanavir-treated subjects. Worst on-study abnormalities of fasting triglycerides and total cholesterol were categorized. Fasting triglyceride abnormalities were comparable across treatment regimens; at most 2% of subjects had fasting triglycerides $\geq$ 751 mg/dL. Nine percent of NFV-treated subjects had total cholesterol $\geq$ 300 mg/dL compared with at most 3% of atazanavir-treated subjects. These changes are discussed in detail under the Special Safety Considerations section of this review.

The number of subjects with elevated amylase, lipase, creatinine and serum uric acid was comparable across treatment regimens and most abnormalities were grade 1 - 2. Fasting

hypoglycemia and hyperglycemia were comparable across treatment regimens; at most 4% of subjects had a glucose abnormality ≥ 161 mg/dL.

White blood cell (WBC) and neutrophil abnormalities were the most frequent hematologic abnormalities across treatment regimens (28% - 41% for WBC and 20% - 33% for neutrophil). The highest incidence of hematologic abnormalities occurred in the NFV treatment regimen. Most hematologic abnormalities were grade 1 - 2. An assessment of potential causes of hyperbilirubinemia including hemolysis was performed via haptoglobin and reticulocytes measurements; haptoglobin and reticulocyte values were comparable in all treatment arms.

Lipodystrophy
Analysis of changes in waist-to-hip ratios through week 48 of treatment did not indicate any clinically significant changes. The incidence of patient and investigator-reported lipodystrophy events was similar between treatment arms (about 4% for all atazanavir treated subjects versus 4% for nelfinavir-treated subjects).

Lactic Acidosis Syndrome
Ten subjects developed lactic acidosis syndrome: 8/310 (2.6%) on atazanavir, for 22.6 cases per 1000 patient years and 2/100 (2.0%) on NFV for 17.5 cases per 1000 patient years. Three of the 10 subjects died (two on atazanavir and one on NFV). Several of the subjects presented with other events consistent with mitochondrial toxicity such as pancreatitis and/or hepatotoxicity. Most patients had risk factors for the development of lactic acidosis (female gender, obesity, pregnancy). The overall rates by gender were 8 (5.3%) of 150 in females and 2 (0.7%) of 270 in males. These events tended to occur at about 40 weeks or later in treatment).

Study AI424041 (041) - This was a multicenter, multinational, active controlled, open-label, extended-dosing rollover study. After treatment assignments were unblinded, subjects who received ATV during the prior study continued to receive ATV after entry into study 041 and subjects who received a comparator continued to receive comparator. Open-label ATV was administered at a dose of 400 mg QD in 041, regardless of the dose administered on the prior study; however, exceptions were made for subjects who required dose modification on the prior study. Additionally, subjects who enrolled from study 009 [a study of treatment-experienced subjects] were allowed to continue on their previous ATV dose. Dosing of the comparator regimen was consistent with the prior study.

Successful study completion was required for enrollment into 041. This was based on investigator judgment of study medication and treatment compliance (as a guide, < 10% missed doses or visits) and adequate viral suppression (HIV RNA < 10,000 c/mL) at the time of study entry.

The presented results represent median ATV dosing of 24 weeks and median NFV dosing of 25 weeks on study 041. The term "baseline" refers to the period immediately prior to

dosing in the previous study. The term "entry" is used to define the study period at entry into study 041, which may encompass the final visit from the prior study.

Subject Disposition for Subjects Randomized in Study 007					
	Number (%) of Subjects				
	ATV 200	ATV 400	ATV 500	NFV	Total
	N = 104	N = 103	N = 110	N = 103	N = 420
Randomized 007	104	103	110	103	420
Discontinued 007	41 (39)	36 (35)	37 (34)	43 (42)	157 (37)
Completed 007	61 (59)	65 (63)	70 (64)	57 (55)	253 (60)
Enrolled in 041	49 (47)	48 (47)	57 (52)	49 (48)	203 (48)
Discontinued 041	4 (4)	3 (3)	3 (3)	5 (5)	15 (4)
Continuing on Treatment	45 (43)	45 (44)	54 (49)	44 (43)	188 (45)

Subject Disposition for Subjects Randomized in Study 009				
	Number (%) of Subjects			
	ATV 400	ATV 600	SQV/RTV	Total
	N = 34	N = 28	N = 23	N = 85
Randomized on 009	34	28	23	85
Discontinued 009	21 (62)	17 (61)	15 (65)	53 (62)
Completed Study 009	11 (32)	10 (36)	8 (35)	29 (34)
Enrolled in Study 041	9 (26)	6 (21)	4 (17)	19 (22)
Discontinued Study 041	1 (3)	1 (4)	0 (0)	2 (2)
Continuing on Treatment	8 (24)	5 (18)	4 (17)	17 (20)

Adverse Events for Subjects who Enrolled from Study 007 into Study 041

The overall incidence of AEs in the 007 cohort was comparable between the ATV treatment regimen and the NFV regimen. In the ATV group, 69% of subjects reported at least one AE versus 59% subjects in the NFV group. The majority of all AEs were mild to moderate (grade 1 - 2) in intensity. Grade 3 - 4 events occurred with a similar frequency in both regimens (7% and 6% on the ATV and NFV regimens, respectively). The most common AE of any grade was infection (22% ATV; 18% NFV). Jaundice was reported in 6% of ATV-treated subjects and in none of the NFV-treated subjects. Nausea and abdominal pain were reported in 5% of ATV-treated subjects and in 0% of NFV-treated subjects. No new type of adverse event was observed with longer-term dosing of ATV.

Deaths

One death of an ATV-treated subject occurred during study 041 prior to database lock. This death was due to unspecified causes, as the patient died at home and no autopsy was performed. However, the subject reported abdominal pain and symptoms of chest infection prior to his death. The investigator considered the death to be unrelated to ATV.

Serious Adverse Events

A total of 16 subjects reported at least one serious adverse event: 13 (8%) of 154 subjects on the ATV regimen, 3 (6%) of 49 on the NFV regimen. Serious adverse events probably

related to therapy with atazanavir included one event of severely prolonged PR interval and bifascicular block due to drug overdose that resolved with withdrawal of treatment, and one event of hyperbilirubinemia.

Adverse Events Leading to Discontinuation from Therapy
A total of five subjects receiving atazanavir and two subjects receiving nelfinavir discontinued therapy for adverse events. For atazanavir-treated subjects adverse events included one event of grade 4 hyperbilirubinemia, one event of sinus headache, one event of peripheral neuropathy, one event of hyperbilirubinemia, and one event of anemia in a subject receiving AZT instead of d4T.

Laboratory Abnormalities
Total bilirubin (predominantly indirect, unconjugated) was the most frequent laboratory abnormality on the ATV regimen (76% with grade 1 - 4 and 18% with grade 3 - 4). The incidence of all grades of transaminase abnormalities was similar between ATV and NFV-treated subjects (about 28% ALT elevations on each regimen). Three ATV-treated subjects and none of the NFV-trated subjects experienced grade 3-4 elevation of ALT. Only one (< 1%) ATV-treated subject had concurrent elevations of total bilirubin, AST, and ALT. This subject concurrently experienced grade 3 bilirubin, grade 4 ALT, and grade 3 AST. This subject had these abnormalities at the time of an acute hepatitis C infection.

No new pattern of hematologic toxicities was identified with long-term dosing of ATV. There were no meaningful differences between the treatment groups in the incidences of serum chemistry abnormalities.

Study AI424008 (008) - This study randomized 467 antiretroviral/naïve HIV-infected subjects and was an active-controlled, three arm study designed to evaluate and compare the safety, tolerability, and antiviral efficacy of atazanavir at two different doses with NFV, in combination with d4T and 3TC through 48 weeks in antiretroviral naïve subjects who had a CD4 cell count ≥□ 100 cells/mm3 (or ≥□75 cells/mm3 with no prior history of any AIDS-defining diagnoses) and a plasma HIV RNA ≥ 2000 c/mL. The dose of atazanavir was blinded.

Clinical Adverse Events
Clinical adverse events were reported frequently with 91% - 93% of treated subjects across all regimens reporting at least one adverse event of any grade. The rates of grade 3 - 4 events were comparable across all treatment regimens (14% - 17%).

The most frequently reported adverse events were infection (42% - 55%), diarrhea (15% - 56%), headache (25% - 27%), nausea (18% - 21%), abdominal pain (13% - 22%), peripheral neurologic symptom (18% - 22%), and rash (17% - 22%). Diarrhea, a well-recognized side effect of NFV, was reported by more subjects (56%) in the NFV regimen compared to subjects (15% - 20%) in the atazanavir regimens ($p < 0.0001$). Jaundice and scleral icterus were reported only by subjects in the atazanavir regimens. Other adverse events were comparable across treatment regimens.

Deaths
There were three deaths reported during the study. One atazanavir 400 mg subject died from suicide 77 days into the study. The remaining two deaths in the atazanavir 600 mg regimen were considered to be related to lactic acidosis.

Serious Adverse Events
Serious adverse events occurred with a frequency of 9% - 13% of subjects, comparable across treatment regimens. The majority of serious adverse events were judged to be unrelated to the protease inhibitor by the investigators. One symptomatic hyperlactatemia case and five lactic acidosis cases occurred only on the atazanavir treatment regimens. Serious adverse events potentially related to atazanavir therapy include one event of allergic reaction, and one event of hyperbilirubinemia.

Adverse Events Leading to Discontinuation of Study Therapy
Twenty-seven (6%) subjects (9 in the atazanavir 400 mg regimen; 14 in the atazanavir 600 mg regimen; 4 in the NFV regimen) discontinued due to one or more adverse events. Overall, these 27 subjects reported 47 adverse events as reasons for discontinuation and 39 of these adverse events were considered at least possibly related to study drug.

One atazanavir 600 mg subject discontinued for hypertriglyceridemia. Four atazanavir subjects (two 400 mg and two 600 mg) discontinued due to lactic acidosis or hyperlactatemia. Four atazanavir 600 mg subjects discontinued due to hyperbilirubinemia. Two atazanavir subjects (one 400 mg and one 600 mg) discontinued as a result of lipodystrophy.

Seven atazanavir subjects (2%) and two nelfinavir subjects (2%) discontinued for abnormal liver enzyme tests. Of the seven atazanavir subjects, five had chronic hepatitis C, one had acute hepatitis B and one had no apparent risk factors for hepatotoxicity. The two nelfinavir subjects had chronic hepatitis C.

Lactic Acidosis Syndrome
Seven subjects (3 in atazanavir 400 mg; 4 in atazanavir 600 mg) developed lactic acidosis syndrome, for 19.6 cases per 1000 subject years, and two of these subjects died (both on atazanavir 600 mg). Several of these presented as part of a syndrome of other mitochondrial related disorders including pancreatitis and hepatotoxicity. All subjects who developed lactic acidosis were female and all but one were overweight (BMI > 25) or obese (BMI > 30), both previously identified risk factors for lactic acidosis in subjects receiving NRTIs. These events tended to occur after at least 30 weeks of therapy.

Hematology
White blood cell (WBC) and neutrophil abnormalities were the most frequent hematologic abnormalities across treatment regimens (29% - 37% for WBC and 20% - 31% for neutrophil). The highest incidence of hematologic abnormalities occurred in the NFV treatment regimen. Most hematologic abnormalities were grade 1 - 2. An assessment of potential causes of hyperbilirubinemia including hemolysis was performed

via haptoglobin and reticulocytes measurements; haptoglobin and reticulocyte values were comparable across all treatment arms.

Other Lab Abnormalities

Overall, creatinine elevations, hypercarbia, hypocarbia and serum uric acid elevations were infrequent across treatment regimens. Elevations in CPK were observed more frequently in the atazanavir regimens (27% - 28%) than in NFV (18%).

Lipodystrophy

Four percent of atazanavir treated patients and two percent of nelfinavir treated patients reported any lipodystrophy event, although mean waist-to-hip ratios were unchanged at week 48.

Study AI424044 (044)

This was an open-label (initially blinded to ATV dose), roll-over/switch study designed to assess the impact on lipid concentrations in subjects who switched from NFV to ATV and to assess longer term safety and antiviral activity in HIV-infected subjects who had completed participation in study 008. Subjects originally assigned to ATV received the same drug regimen that they received in study 008 (i.e., ATV 400 mg/d4T/3TC or ATV 600 mg/d4T/3TC), including any previous ATV dose reduction due to bilirubin elevation or previous changes in NRTIs. Subjects originally assigned to NFV received ATV 400 mg in combination with d4T/3TC or previously changed NRTIs. Eligible subjects were those who had completed study 008, with a plasma HIV RNA viral load < 10,000 c/mL, and who, in the investigator's opinion, had demonstrated compliance with the study medication and treatment visits. A total of 346 subjects were enrolled.

Subject Disposition for Subjects Randomized in Study 008			
	Number (%) of Subjects		
	ATV 400	ATV 600	NFV to ATV
	N = 181	N = 195	N =91
Randomized 008	181	195	91
Discontinued 008	31	42	22
Completed 008	147	153	69
Enrolled in 044	139	144	63
Discontinued 044	12	9	6
Continuing on Treatment	127	135	57

In general, the long-term safety profile of the ATV-treated subjects was consistent with that observed in study AI424008. The incidence of AEs was comparable among the treatment cohorts (ATV 400, 68%; ATV 600, 74%; NFV to ATV, 79%). Grade 3 - 4 AEs occurred in 4-6% of subjects.

The most common adverse events of any grade that were reported with a comparable incidence among the treatment cohorts were, lipodystrophy, abdominal pain, rash, peripheral neurologic symptoms, jaundice, scleral icterus, and nausea.

Adverse events that occurred with a higher frequency in the NFV to ATV cohort as compared to the ATV 400 and ATV 600 cohorts included headache [19% vs. 9% and 6%, respectively $p < .05$)], fatigue (6% vs. 1% and 2%, respectively), and fever (5% vs. 1% and 3%, respectively).

Ten percent of enrolled subjects reported jaundice or scleral icterus. Combining data from study 008 and study 044, jaundice was reported more frequently in the ATV 600 cohort (22%) as compared to the ATV 400 cohort (13%). The incidence of scleral icterus and scleral jaundice was comparable between the two cohorts (ATV 400, 10% and < 1%, respectively; ATV 600, 13% and < 1%, respectively).

Deaths
There was one death reported during the study, in a subject in the NFV to ATV cohort. A 71 year-old male, died on study day 802 following hospitalization for severe congestive heart failure with atrial flutter, renal failure, rhabdomyolysis, metabolic acidosis, and dehydration which the investigator judged as unrelated to study medications. The subject died from cardiac arrest.

Serious Adverse Events
Serious adverse events were experienced by a total of eleven subjects. All of these events were judged by the Investigators to be unrelated or not likely related to study therapy.

Adverse Events Leading to Discontinuation of Study Therapy
A total of seven subjects discontinued for adverse events; these included one event of scleral icterus, one event of lipodystrophy and one event of weight loss.

Laboratory Abnormalities
In general, laboratory abnormalities were comparable among treatment regimens. The incidence of grade 1 - 4 liver transaminase elevations was comparable among the treatment cohorts; grade 3 - 4 liver transaminase elevations were infrequent in all treatment cohorts (≤ □2%). There were no subjects with concurrent grade 3 - 4 bilirubin and grade 3 - 4 ALT or AST elevations during study therapy.

Five subjects (one ATV 400 and four ATV 600 subjects) experienced grade 4 elevation in bilirubin; there were no grade 4 elevations in bilirubin among subjects in the NFV to ATV cohort. Among the five subjects with Grade 4 hyperbilirubinemia, two subjects in the ATV 600 cohort were dose-reduced. In addition, one subject in the ATV 600 cohort was noted to have grade 4 elevation in bilirubin at the final visit for study 008 and was on study 044.

Study AI424009 (009) - This study was a multinational, active-controlled three arm study designed to evaluate and compare the safety, tolerability, and antiviral efficacy of ATV/SQV at two different doses to RTV/SQV, each in combination with two NRTIs, through 48 weeks in antiretroviral-experienced subjects with CD4 cell count ≥□100 cells/mm3 (or ≥□75 cells/mm3 in subjects with no prior history of any AIDS-defining

diagnosis) and plasma HIV RNA level ≥□1,000 c/mL. A total of 85 antiretroviral experienced HIV-infected subjects were randomized.

This study was blinded only to atazanavir dose. The dual protease combinations were administered with two NRTIs: didanosine (ddI), stavudine (d4T), lamivudine (3TC) or zidovudine (ZDV) in combination as ddI + d4T, d4T + 3TC, ddI + ZDV or 3TC + ZDV. The selection of NRTIs was based on the phenotypic susceptibility data for the subject's viral isolate obtained at the screening visit and the physician's choice at the time of randomization.

The incidence and type of on-study adverse events were comparable across treatment regimens with the exception of diarrhea and jaundice; diarrhea was reported more frequently with the RTV/SQV regimen than either atazanavir/SQV regimen (48% vs 7% - 31%, respectively). Jaundice was reported only in atazanavir/SQV recipients at a frequency of 13% - 15%. A total of four cases of lipodystrophy were reported, two with the RTV/SQV regimen and two with the atazanavir 600 mg/SQV regimen. There were no deaths.

The rate of discontinuation prior to week 48 was higher with the RTV/SQV regimen than either ATV/SQV regimen (52% vs 24% - 29%, respectively), with more discontinuations due to adverse events with RTV/SQV (30% vs 9% - 11%, respectively). Eight subjects receiving ATV containing regimens discontinued treatment; reasons for discontinuation included one event of jaundice, one event of diarrhea, and two events of nausea with or without vomiting.

One subject who received the atazanavir 400 mg/SQV regimen and 4 subjects who received the atazanavir 600 mg/SQV regimen required dose reduction during the study, which was protocol mandated for an increase in total bilirubin.

Hyperbilirubinemia was the most frequently observed laboratory abnormality, and was more common with the ATV/SQV regimens than the RTV/SQV regimen (81% - 91% vs 18%, respectively). Grade 3 – 4 hyperbilirubinemia with the ATV/SQV regimen was dose related (48% with ATV 600/SQV and 22% with ATV 400/SQV). Grade 3 - 4 elevations in ALT/AST were observed more frequently with the RTV/SQV regimen than with either atazanavir/SQV regimen (23% vs 3 - 15%, respectively).

Despite co-administration with SQV, subjects receiving ATV/SQV had concentrations of total cholesterol, fasting LDL cholesterol, and fasting triglycerides that remained essentially stable regardless of dose. By contrast, subjects receiving RTV/SQV experienced pronounced increases over baseline in these lipid concentrations through the 48-week treatment period. HDL cholesterol concentrations rose modestly across regimens.

Study AI424034 (034)

As previously mentioned, study 034 was a multinational, randomized, double-blind, double-dummy, active-controlled, two-arm study comparing atazanavir to efavirenz for

the treatment of ARV-naïve subjects. Each drug was administered with fixed dose AZT/3TC. Subjects were treated through 48 weeks. Enrollment criteria included CD4 count > 100 and viral load > 2000 copies/mL.

The overall incidence of AEs was comparable between the two treatment regimens. At least 95% of all subjects on both treatment regimens reported at least one adverse event. The majority of all AEs were mild to moderate. Grade 3 - 4 events occurred with a comparable frequency in both regimens (15% and 17% on the ATV and EFV regimens, respectively).

The most common adverse events of any grade that were reported with a comparable incidence on both treatment regimens were infection (50% ATV; 52% EFV), nausea (46% ATV; 43% EFV), headache (30% ATV; 31% EFV), vomiting (20% ATV; 18% EFV), diarrhea (18% ATV; 20% EFV), pain abdomen (17% ATV; 16% EFV), somnolence (11% ATV; 15% EFV), insomnia (10% ATV; 14% EFV), and fever (13% ATV; 15% EFV).

The most frequent grade 3 - 4 adverse events reported on the ATV regimen were jaundice (2%) and nausea (2%). The most frequent grade 3 - 4 adverse events reported on the EFV regimen were rash (3%) followed by vomiting (2%).

Adverse events that occurred with a higher frequency on the ATV regimen, included jaundice (11% vs. 0%), scleral icterus (11% vs. 2%), and ulcer mouth (5% vs. 1%). Adverse events that occurred with a higher frequency on the EFV regimen included some CNS symptoms: dizziness (39% vs. 13%), abnormal dreams (10% vs. 6%), nervousness (3% vs. < 1%), rash (29% vs. 23%), and vasodilatation (7% vs. 3%).

At 48 weeks one case of lactic acidosis syndrome had been reported in each treatment arm.

Deaths

There were five deaths reported during the study, two on the ATV regimen and three on the EFV regimen. All deaths were considered unrelated to study therapy. Three of the five deaths occurred after the discontinuation of study therapy. Reported causes of death included one case each of TB meningoencephalitis, pulmonary TB, lung cancer, pneumonia with brain edema, and homicide.

Serious Adverse Events

Serious adverse events occurred in 10% of patients on both treatment regimens. Events potentially related to study therapy were consistent with previously identified side effect profiles of each of the study drugs.

Anemia was reported more frequently in atazanavir treated subjects versus efavirenz (9 versus 4 subjects), however, grade 3-4 hemoglobin abnormalities were comparable between treatment regimens (3-4%). In addition, anemia is an adverse event often attributable to AZT therapy.

Two cases of rash and one event of Stevens Johnsons syndrome were reported in efavirenz-treated subjects and in none of atazanavir-treated subjects.

Two events of jaundice in atazanavir patients were reported as adverse events.

Adverse Events Leading to Discontinuation of Study Therapy
Sixty-five subjects discontinued therapy because of adverse events; 7% of subjects on the ATV regimen and 9% on the EFV regimen. The most frequent events leading to discontinuation in the atazanavir treated group were anemia (2%), nausea (1%) and vomiting (1%). Scleral icterus and jaundice led to two and one subjects discontinuing treatment, respectively, on the ATV regimen. The most frequent events leading to discontinuation on the efavirenz regimen were rash (2%) and nausea (1%). Three (<1%) patients receiving atazanavir discontinued for rash.

The incidence of on study AIDS events was infrequent and similar between the two treatment regimens.

Laboratory Adverse Events
More laboratory abnormalities were reported as adverse events on the ATV treatment regimen (26% vs. 18%). The higher incidences on the ATV regimen mainly reflected a higher incidence of events in the metabolic system (specifically hyperbilirubinemia, 8% vs. 0%). A slightly higher incidence of anemia and leukopenia was reported on the ATV regimen compared to the EFV regimen (9% ATV; 6% EFV and 4% ATV; 2% EFV, respectively).

Study AI424043 (043) - General Safety Issues
The incidence of AEs was slightly less frequent on the ATV treatment regimen (69%) as compared with the LPV/RTV treatment regimen (77%). The majority of AEs were mild to moderate (Grade 1 - 2) in severity; Grade 3 - 4 adverse events were observed in approximately 10% of subjects in each treatment regimen.

The most common adverse events of any grade that were reported with a comparable incidence between the treatment regimens were headache, nausea, peripheral neurologic symptoms, abdominal pain, fatigue, insomnia, vomiting, and lipodystrophy.

Adverse events that were observed more frequently on the ATV treatment regimen as compared with the LPV/RTV treatment regimen included rash (ATV, 13%; LPV/RTV, 7%), dizziness (ATV, 8%; LPV/RTV, 3%), extremity pain (ATV, 8%; LPV/RTV, 1%), jaundice (ATV, 10%; LPV/RTV, 0%), and scleral icterus (ATV, 6%; LPV/RTV, 0%).

Adverse events that were observed more frequently on the LPV/RTV treatment regimen as compared with the ATV treatment regimen included infection (ATV, 35%; LPV/RTV, 40%), diarrhea (ATV, 10%; LPV/RTV, 32%), somnolence (ATV, 3%; LPV/RTV, 9%), and anorexia (ATV, < 1%; LPV/RTV, 5%).

Grade 3 - 4 jaundice occurred in 3 subjects (2%) on the ATV treatment regimen and was not reported on the LPV/RTV treatment regimen. One subject discontinued due to jaundice or scleral icterus, and three subjects dose reduced for hyperbilirubinemia or unacceptable jaundice.

Deaths
One death due to homicide was reported during the 24 week study period.

Serious Adverse Events
Serious adverse events (SAEs) were infrequent and evenly distributed between the treatment arms. A total of 15 enrolled subjects reported at least one SAE (ATV, 9 subjects; LPV/RTV, 6 subjects). The events on both treatment regimens were consistent with the known side effect profile of the study drugs and the nucleoside backbone therapy. SAEs potentially related to study therapy included one event each of pancreatitis; jaundice, hyperglycemia, and liver damage in atazanavir-treated patients.

Adverse Events Leading to Discontinuation of Study Therapy
Discontinuation of study therapy due to adverse events was infrequent on both treatment regimens (ATV, 2 subjects; LPV/RTV, 4 subjects). Overall, these six subjects reported 13 adverse events as reasons for discontinuation. One atazanavir subject discontinued for juandice and abnormal LFTs and one subject discontinued for lipoatrophy and scleral icterus.

7.5 Miscellaneous Studies

The following studies either enrolled small numbers of patients or had insufficient follow-up to be utilized in the primary review of this NDA. Selected safety findings will be highlighted in the reviews of these NDAs.

Study AI424037 (037)
This was a multicenter, multinational, randomized, double-blind, double-dummy, active-controlled study, with two parallel groups of study subjects who received either ATV or NFV, each in combination with two NRTIs. Antiretroviral-experienced HIV-infected subjects who received no, or limited, prior protease inhibitor (PI) therapy, who were failing a current regimen, and who had a plasma HIV RNA ≥ 1000 c/mL and CD4 cell count of ≥ 50 cells/mm^3 were enrolled into the study. Thirty subjects were randomized in the study, 15 to each treatment arm.

The planned study duration was 48 weeks. Due to lack of enrollment, the study was terminated prematurely. Duration of treatment of subjects was variable, with a maximum dosing duration of 25 weeks.

Two (2%) of the 30 randomized subjects experienced a serious adverse event (SAE) during the study: one subject in the NFV group had a syncopal event and one subject in the ATV group reported gastritis. This syncope was not associated with any reported ECG abnormalities.

No deaths were reported during the study. One subject receiving NFV concomitantly with methadone discontinued from study participation due to an adverse event (QT interval prolongation). None of the ATV-treated subjects discontinued study therapy due to an AE. No other clinically significant ECG abnormalities were observed. Two of the fifteen atazanavir subjects experienced grade 3-4 elevations of total bilirubin.

Study AI424038 (038)
This study is a phase 2 multicenter, observational, open-label pilot study of the safety and efficacy of enteric coated didanosine, stavudine and atazanavir, administered early in the course of HIV infection, with regard to the ability to reduce replication of HIV-1 in plasma and tissues to undetectable levels and to sustain absence of detectable replication of HIV-1 in the plasma and tissues for a duration of 48 weeks. Subjects choosing to receive ARV treatment are considered group 1, and will receive the following oral treatment: ddI EC 400mg QD + d4T BID + atazanavir 600mg QD. A small number of subjects who are eligible and agree to be followed in the study but who elect not to receive any antiretroviral treatment will be enrolled and will serve as a natural history cohort (Group 2).

At the time of this NDA submission, 34 subjects had received a mean duration of 41 weeks of therapy. Three subjects discontinued for one event each of hyperbilirubinemia, medication change, and lost to follow-up, and 31 were continuing on study.

Serious adverse events reported by subjects that were potentially related to study therapy included nine events of hyperbilirubinemia and two events of elevated ALTs.

Grade 3-4 elevations of total bilirubin were reported in 23/34 (68%) of subjects, grade 3-4 ALT was reported in 2/34 (6%) of subjects and grade 3-4 neutropenia was reported in one subject.

Study AI424045 (045)
Study 045 is a randomized, multinational, open-label, active-controlled, three arm study of highly treatment-experienced patients who had failed at least two ARV regimens containing drugs from all three classes at the time of enrollment. A total of 357 patients were randomized in this study. Data on efficacy through 16 weeks of therapy for approximately 100 subjects was submitted with the NDA. Sixteen week efficacy and safety data for all randomized subjects was submitted with a safety update provided two months into the six month review clock; this data was reviewed for safety, but not specifically for efficacy.

Clinical adverse events were common in study subjects, and occurred in 71 - 79% of all subjects. The most frequently reported adverse events of any grade were diarrhea (16 - 42%), infection (21 - 31%), nausea (10 - 20%), headache (12 - 18%), abdominal pain (5 - 19%), and jaundice (0 - 15%).

Diarrhea was reported by more subjects who received LPV/RTV (42%) compared to subjects receiving ATV 300/RTV (16%) and ATV 400/SQV (22%). Nausea and abdominal pain were reported more frequently on the ATV 400/SQV treatment regimen (about 20% each) compared to the ATV 300/RTV (13% and 6%) and LPV/RTV regimens (10% and 5%). Jaundice and scleral icterus were reported in 15% and 9% of ATV/RTV treated patients and in 5% and 3% of ATV/SQV treated patients; these events were not reported in the LPV/RTV treated patients. Other adverse events, including lipodystrophy, were comparable across treatment regimens.

Grade 3 - 4 events occurred more frequently on the ATV 400/SQV regimen (13%) compared to the ATV 300/RTV (5%) and LPV/RTV (7%) regimens. The most frequent Grade 3 - 4 adverse events were reported in the digestive and nervous systems on the ATV 400/SQV (6%) and LPV/RTV treatment regimens (4%), respectively.

Deaths
There was one death, due to subdural hematoma, that was reported on the LPV/RTV regimen and was considered unrelated to study therapy.

Serious Adverse Events
A total of 26 randomized subjects reported at least one SAE: eight (7%) on the ATV 300/RTV regimen, 10 (9%) on the ATV 400/SQV, and eight (7%) on the LPV/RTV regimen. No SAE was reported in greater than 1% of treated subjects.

SAEs potentially related to study therapy included one event of hyperglycemia in an ATV/RTV treated patient.

Adverse Events Leading to Discontinuation of Study Therapy
Thirteen subjects discontinued therapy because of adverse events: four subjects on the ATV 300/RTV regimen, five subjects on the ATV 400/SQV regimen, and four subjects on the LPV/RTV regimen. Events leading to study drug discontinuation occurred infrequently and were comparable across all three regimens. The most frequent events leading to discontinuation on the ATV 400/SQV regimen were nausea (2%) and vomiting (2%) while the events leading to discontinuation on the ATV 300/RTV were reported less frequently (< 1%). One subject receiving ATV/RTV and one subject receiving ATV/SQV discontinued for allergic reaction/rash. No subjects discontinued treatment due to scleral icterus and/or jaundice.

Laboratory Abnormalities
Hematologic abnormalities were generally comparable among treatment regimens and most were grade 1-2. Grade 3-4 abnormalities were infrequent and comparable between regimens. The most common hematologic abnormalities reported were grade 1-4 WBC abnormalities (29-39%) followed by neutropenia (12-21%).

The majority of liver function test abnormalities on study were grade 1-2. More grade 1-4 ALT elevations were observed on the ATV-containing regimens compared to the LPV/RTV regimen (ATV 300/RTV, 43%; ATV 400/SQV 48%; LPV/RTV 28%),

however, the number of study subjects with grade 3-4 ALT elevations was similar between regimens (3% on all regimens).

Among subjects co-infected with Hepatitis B or C, the frequency of treatment emergent Grade 3 - 4 ALT elevations was higher on the ATV 300/RTV (n=3, 15%) and ATV 400/SQV (n=2, 11%) treatment regimens compared to the LPV/RTV treatment regimen (n=1, 6%).

The mean and median total bilirubin of ATV/RTV treated subjects at 16 weeks was 2.14 and 1.70 mg/dL, respectively. the mean and median total bilirubin of ATV/SQV treated subjects was 1.34 and 1.10 mg/dL, respectively. The protocol recommended dose reduction for management of grade 4 hyperbilirubinemia or unacceptable jaundice. Eleven (3%) ATV-treated subjects experienced a grade 4 elevation in bilirubin; seven of the eleven had their dose reduced.

Two subjects on the ATV/RTV treatment regimen and one subject on the ATV/SQV treatment regimen experienced both Grade 3 - 4 bilirubin and Grade 3 - 4 ALT or AST levels during study therapy compared to no subject on the LPV/RTV regimen. These elevations appeared to be transient, and in one case, may have been due to alcohol abuse.

The majority of serum chemistry abnormalities were Grade 1 - 2 and comparable across treatment regimens. Grade 1 - 4 hypocarbia was reported most frequently (ATV/RTV: 31%; ATV/SQV: 31%; LPV/RTV: 30%) followed by lipase and creatinine kinase (CK) abnormalities.

Lipids and Glucose

Baseline mean total cholesterol was slightly higher on the ATV/RTV regimen (ATV 300/RTV, 188 mg/dL; ATV 400/SQV, 175 mg/dL; LPV/RTV, 181 mg/dL). At 16 weeks, decreases in total cholesterol were observed for ATV-treated subjects (ATV 300/RTV: -7%; ATV 400/SQV: -10%), while LPV/RTV-treated subjects experienced a 5% increase in total cholesterol. These differences were statistically significant.

Baseline mean fasting triglyceride levels were higher on the ATV/SQV regimen (253 mg/dL) as compared to ATV/RTV (215 mg/dL) and LPV/RTV (197 mg/dL) regimens. At 16 weeks, a mean decrease in triglycerides of 15% was observed on the ATV 400/SQV regimen, a minimal increase of 2% was observed on the ATV 300/RTV regimen, and an increase of 34% was observed on the LPV/RTV regimen. These differences were also statistically significant.

Decreases from baseline in mean fasting LDL cholesterol at week 16 were observed for ATV containing regimens (ATV 300/RTV -8%; ATV 400/SQV-11%), while no significant change was observed for the LPV/RTV regimen (1%). Only the difference between ATV/SQV and LPV/RTV regimens reached statistical significance.

At week 16, small mean decreases in HDL cholesterol were observed on ATV/RTV (-6%) and ATV /SQV (-5%) regimens, while no change was seen on the LPV/RTV regimen.

Approximately twice as many subjects on the ATV 300/RTV and LPV/RTV regimens experienced any grade hyperglycemia on study as compared with the ATV 400/SQV regimen (16% compared to 8%). One subject on ATV 300/RTV was hospitalized on day 41 for increased blood sugar. The event resolved and the investigator judged the event to be probably related to study therapy.

QT Intervals
A QTc interval measurement of > 450 msec was observed with similar frequency in male subjects on each regimen (3%, 5%, 3% for ATV 300/RTV, ATV 400/SQV and LPV/RTV respectively). One female subject in each of the ATV 400/SQV and LPV/RTV regimens, had a post-dose QTc interval measurement > 470 msec (< 1% for each regimen). No on-study QTc measurements > 500 msec were observed.

One (<1%), four (4%) and one (<1%) male subjects in the ATV 300/RTV, ATV 400/SQV and LPV/RTV regimens respectively, and no female subjects experienced a change in QTc from baseline of > 60 msec.

PR Intervals
Baseline measurements were comparable among all three treatment regimens. Minimal increases in the mean PR interval change from baseline were observed at week 4 among all regimens. Mean PR interval recorded across all timepoints on each regimen at 4 weeks was 154 msec (ATV/RTV), 160 msec (ATV/SQV), and 156 msec (LPV/RTV).

Five percent of subjects on each treatment regimen experienced first degree AV block (PR > 200 msec) on at least one post-baseline ECG. The longest PR interval recorded in ATV-treated subjects was 252 msec and the longest PR interval recorded in LPV/RTV-treated subjects was 271 msec.

Heart Rate
Heart rates of atazanavir-treated subjects appeared to be slightly higher than LPV/RTV-treated subjects at week 4, however, at week 12, heart rates appeared to be similar to baseline heart rates.

Study AI424049 (049)
This study is an observational, open-label study with subjects recruited from existing ——— clinical trials. Eligible subjects were those who had achieved and maintained HIV RNA viral loads below the limit of quantification of ——— on their current PI/dual NRTI containing regimens. Subjects were randomized into two arms, either intensive adherence intervention or control. All subjects received once daily therapy with atazanavir (400 mg), lamivudine (300 mg), and extended release stavudine (100 mg). The mean duration on treatment of study subjects was 70.3 weeks (range 33 - 79.5).

At the time of submission of this study report, 23 subjects had been enrolled. Five subjects had discontinued treatment and 18 were continuing on study. One subject each had discontinued for grade 4 ALT/AST, lipodystrophy, virologic failure, withdrawal of consent, and lost to follow-up. One subject experienced grade 4 neutropenia 8 weeks after starting study medications; treatment was interrupted for 4 weeks and restarted without reoccurence of neutropenia.

Grade 3-4 elevations in total bilirubin were experienced by 11/23 (47%) subjects, grade 3-4 elevations of ALT/AST were experienced by 2/23 (9%) patients, one who discontinued therapy, and grade 3-4 lipase were experienced by 5/23 (22%) of patients.

One subject was hospitalized during the study for angioplasty and one subject was hospitalized on two occasions for treatment of peripheral vascular disease.

Fourteen of the 18 subjects continuing on treatment at the time of this report had switched from extended release stavudine to tenofovir, half for rapidly progressive lipoatrophy, and half at the advice of the investigator.

AI424069 (069)
This first step of this study is a three-arm, randomized blinded treatment phase where treatment-naïve subjects with HIV RNA viral loads greater than 400 copies/mL receive one of the following three regimens:

Arm A: ABC/3TC/ZDV (fixed dose combination) BID + 3TC/ZDV placebo BID + EFV 600 mg QD
Arm B: ABC/3TC/ZDV (fixed dose combination) BID + 3TC/ZDV placebo BID + EFV placebo QD
Arm C: ABC/3TC/ZDV placebo BID + 3TC/ZDV (fixed dose combination) BID + EFV 600 mg QD

Subjects with continued treatment limiting toxicity despite drug holds, dose reductions, and/or drug substitutions proceed to Step 2. Subjects with confirmed virologic failure on Step 1 and whose confirmatory plasma HIV RNA is < 10,000 c/mL may either remain on Step 1 or register to Step 2. Subjects with confirmed virologic failure on Step 1 and confirmed (two successive) plasma HIV RNA levels =10,000 c/mL must register to Step 2. Subjects who choose to remain on Step 1 will be permitted to register to Step 2 at a later date but must have repeat genotypic resistance testing if more than 8 weeks has elapsed. The two open-label treatment options for Step 2 are:

Arm D: 2 NRTIs + EFV 600 mg QD (NVP may be substituted if NVP substitution occurred on Step 1),
Arm E: 2 NRTIs + atazanavir 400 mg QD

At the time of the NDA submission 19 subjects had been enrolled in the atazanavir study arm. Four patients had discontinued, for one event each of allergic reaction, virologic failure, non-compliance with study visits, and one unspecified toxicity.

Reported serious adverse events were two events of hyperbilirubinemia, one event of seizure, and one unspecified toxicity. Reported ECG abnormalities included one event of first degreee AV block.

Three subjects experienced grade 3-4 elevations in total bilirubin, one subject experienced grade 3-4 hypertriglyceridemia, and one subject experienced grade 3-4 hyperglycemia.

Study AI424074 (074) "Therapeutic Trial Assessing the Efficacy and Safety of the Combination of Tenofovir DF and Atazanavir (BMS-232632), Pharmacologically Potentiated by Ritonavir, for Six Months, in HIV- Positive Patients in Multiple Virological Failure"

This is a two step trial designed to assess the efficacy and safety of a regimen containing atazanavir 300 mg QD, ritonavir 100 mg QD, tenofovir 300 mg QD and a combination of 2 NRTIs selected from the results of resistance testing through 26 weeks.

- **STEP ONE** - Day 1 to day 14. Fifty patients randomized between:
  -Group one: Failing PI and NRTIs maintained (n = 25)
  -Group two: atazanavir 300 mg QD combined with 100 mg of ritonavir; failing NRTIs maintained and failing PI stopped (n = 25)
- **STEP TWO** - Day 15 to week 26. Select NRTI backbone according to genotype:
  -Atazanavir 300 mg QD, ritonavir 100 mg QD + tenofovir DF 300 mg QD + optimized NRTIs (n = 50)

The study population was heavily pretreated with a mean duration of previous antiretroviral treatment of eight years. A total of 51 subjects were randomized and 48 received treatment. One subject died from actue cardiac failure prior to receiving study medications. Three subjects discontinued prior to the wek 26 visit.One subject discontinued for ventricular bigeminy that persisted after study medications were discontinued. One subject discontinued for a Fanconi-like syndrome possible secondary to tenofovir, hepatic steatosis and abnormal liver enzyme tests. A third subject also discontinued for a Fanconi-like syndrome.

In addition to the above adverse events that were considered SAEs, one SAE of thrombocytopenia was reported.

The most common adverse events of all grades included diarrhea (23%), nausea (21%), depression (19%), and asthenia (15%). Other reported adverse events potentially attributable to therapy with atazanavir included rash (8%), lipodystrophy (8%), lipoatrophy (4%), jaundice (4%), hepatomegaly (2%), and diabetes (4%).

Any grade abnormality of bilirubin was reported by 70% of subjects, however, notably only one subject reported grade 3 elevation of bilirubin and no subject experienced grade 4 hyperbilirubinemia. There was no difference in the number of subjects with any grade transaminase abnormality prior to or during treatment.

AI424900 (900)– Expanded Access Protocol

Study 900 is an open-label, multicenter, noncomparative, international expanded access protocol. In this program, subjects receive atazanavir 400 mg once daily with food in combination with two or more antiretroviral agents. The additional antiretroviral agents used are selected by investigators based on treatment history and data from genotypic and/or phenotypic resistance testing, when performed. Subjects continue to receive atazanavir until the subject experiences a treatment-limiting toxicity, voluntarily withdraws, dies, becomes lost to follow-up, the subject or the physician determine that the subject is no longer receiving benefit from atazanavir, or termination of the study by the sponsor.

The ATU Nominative is a premarketing authorization program administered by the French Health Authority. Investigators submit a request form to the French Health Authorities (FHA) that in turn authorizes the shipment of study drug. The ATU Nominative program provides atazavanir 400 mg once daily to French subjects who are infected with HIV for use in combination with additional antiretroviral agents. Safety data collected in the ATU Nominative are voluntary and include laboratory measurements, and adverse events (AEs); this safety data is also included in this report.

Of the 639 subjects that demonstrated eligibility, CRF data confirming that study drug was dispensed has been reported for 389 subjects (295 EAP, 94 ATU Nominative) as of the cutoff date for this report. These 389 subjects comprise the treated population.

Thirteen (3%) treated subjects discontinued from the study leaving 376 subjects that are continuing on study. The majority of all treated subjects (356/389, 92%) were male; 27 (7%) treated subjects were female, the gender of 6 (2%) treated subjects was missing. Of subjects with an age reported, the youngest enrolled subject was 21 years old, the oldest subject was 68 years old. Baseline HIV RNA data were available for 373 (96%) of the 389 treated subjects; baseline HIV RNA (log10 copies/mL) levels ranged from 1.3 to 6.3. An absolute CD4 cell count was available for 382 (98%) of the 389 treated subjects at baseline; absolute CD4 cell counts at baseline ranged from 1 to 1364 cells/mm^3. The maximum dosing duration as the data cutoff was approximately 116 days in study 900 and 214 days in the ATU Nominative.

A total of 7 deaths (6 males in the EAP and 1 male in the ATU Nominative) were reported. Causes of death were reported as two events of HIV disease progression (including one subject who never initiated therapy), two events of PCP pneumonia, and one event each of perforated ulcer, cerebral infarct, and aspergillus pneumopathy.

Six subjects discontinued for adverse events reported as one event each of fatigue/bronchitis, rash, fatigue/nausea, GI bleed, drug fever, and HIV disease progression. Other study discontinuations that were reported as SAEs included one event of elevated total and direct bilirubin, one event of drug-induced hepatitis and hepatic steatosis in a patient with chronic hepatitis B, and one event of abdominal pain. One death reported after the data cutoff for this report was a patient hospitalized for junctional rhythm; this patient has been described elsewhere in this review.

A total of 44 SAEs had been reported. The clinical database contained a total of 14 SAEs that occurred on or before 01 November 2002 in 11 (2.8%) treated subjects and narrative for one death.

As of 01 November 2002, 49 (12.6%) treated subjects experienced a total of 78 grade 1-4 nonserious AEs. The most common grade 1-4 nonserious adverse events were: rash (10 subjects, 2.6%), nausea (8 subjects, 2.1%), diarrhea (8 subjects, 2.1%), and flatulence (4 subjects, 1.0%).

A total of 6 (1.5%) treated subjects experienced a total of 7 grade 3 - 4 nonserious AEs. Grade 3-4 adverse events included one event each of dehydration, hypertension, liver damage, abnormal lab, pharyngitis, chest pain, and nausea.

In summary, no new safety concerns have been identified from subjects enrolled in the expanded access program.

7.6 Literature Review for Safety

Reyataz® has not been marketed in any country; therefore, no literature review was conducted for assessment of safety.

7.7 Postmarketing Surveillance

Reyataz® has not been marketed in any country, therefore no postmarketing surveillance has been performed.

7.8 Safety Update

No new safety issues were identified in the Safety Update submitted February 28, 2003. Submitted materials included sixteen week safety data for all randomized subjects in study 045 and pharmacokinetic study report 076; these reports are reviewed in other sections of this review.

7.9 Drug Withdrawal, Abuse, and Overdose Experience

Atazanavir has no potential for drug withdrawal or abuse.

Human experience of acute overdose with atazanavir is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of atazanavir in an HIV-infected patient (73 times the 400-mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation; these events resolved with withdrawal of treatment.

8 Dosing, Regimen, and Administration Issues

At the end of phase 2 clinical trials , the 400 mg once daily dose of atazanavir was chosen over other doses in order to balance efficacy with the dose dependent adverse event of indirect hyperbilirubinemia. In dose finding phase 2 study 008, no significant difference between the 400 mg and 600 mg doses were observed in multiple proportion below the limit of quantification analyses. In study 007 it appeared that more subjects receiving 500 mg achieved undetectable viral loads in a virologic response completers analysis for the limit of quantification of 50 copies/mL, however, this study enrolled fewer subjects than 008.

Atazanavir 400 mg once daily appeared to be similar to efavirenz or nelfinavir in combination with two NRTIs in studies of treatment-naïve patients. However, in a treatment-experienced study, atazanavir 400 mg once daily was inferior to lopinavir/ritonavir at 24 weeks.

A ritonavir-boosted dose of atazanavir (300/100 once daily) is under investigation as a treatment option for highly treatment experienced patients. This dose provides a trough level of atazanavir that is approximately five-fold that of the 400 mg once daily dose. Preliminary safety and efficacy data from phase 3 study 045 indicate that this combination is similar to lopinavir/ritonavir in this highly experienced treatment population. The applicant plans to submit data from this trial in an efficacy supplement.

9. Use in Special Populations

9.1 Efficacy and Safety Analyses of Effects of Gender and Race

Efficacy

Clinical trials were conducted across several continents within a diverse adult population. There was no convincing evidence in treatment-naïve or in treatment-experienced studies that the observed clinical benefit is reduced in any of the racial or gender categories examined.

Safety

Sub-population analyses were performed by the applicant for adverse events of all grades, serious adverse events, adverse events leading to treatment discontinuation, and laboratory test parameters.

Safety Analysis by Gender

In general, men and women experienced comparable AE profiles. Females had higher incidences of the following AEs compared with males: headache (25% vs. 15%) and abdominal pain (21% vs. 8%), whereas males had higher incidences of the following AEs compared with females: peripheral neurologic symptoms (13% vs. 4%), jaundice (12% vs. 4%), and fatigue (11% vs. 4%). Grade 3 - 4 AEs were infrequent for both genders. Males reported a greater than 1% difference compared with females for the following Grade 3 - 4 events: jaundice (2% vs. 0%) and headache (2% vs. 0%). Grade 2 - 4 AEs related to study therapy were reported more frequently in males (25%) than females (12%). The incidence of SAEs was comparable between men and women (males, 9%; females, 7%). Adverse events leading to treatment discontinuation were observed more frequently among males (6%) than females (2%).

Females tended to have more frequent hematologic abnormalities than males (low hemoglobin, 16% vs. 2%; low WBC, 43% vs. 24%). Males were found to have more frequent ALT (41% vs. 28%), AST (38% vs. 26%), CK (21% vs. 13%), amylase (22% vs. 14%), and serum uric acid (11% vs. 1%) abnormalities than females. Males also reported higher incidences of total cholesterol (51% vs. 39%) and triglyceride (40% vs. 13%) abnormalities and hyperglycemia (17% vs. 7%) than females.

Race

Asian/Pacific Islanders had higher incidences of headache (38% vs. 11% - 22%), lipodystrophy (15% vs. 4% - 9%), fever (15% vs. 6% - 7%), and allergic reaction (15% vs. 0% - < 1%) than other racial groups. Asian/Pacific Islanders also reported a higher incidence of Grade 2 - 4 treatment related headache (23% vs. 0% - 5%).

Hispanic/Latinos had higher incidences of any grade back pain (10% vs. 0% - 4%) and insomnia (11% vs. 0% - 6%) than other racial groups. White subjects had a higher incidence of any grade nausea (18% vs. 0% - 13%) and abdominal pain (16% vs. 7% - 8%) than other racial groups. Black/mixed subjects had a higher incidence of any grade vomiting (11% vs. 0% - 9%) and increased cough (13% vs. 0% - 6%) than other racial groups.

In general, there were no discernable differences among racial groups for SAEs or adverse events leading to treatment discontinuation.

Black/mixed subjects had higher incidences of hemoglobin (13% vs. 0% - 5%), WBC (40% vs. 8% - 32%), neutrophil (33% vs. 8% - 18%), CK (31% vs. 8% - 19%), and serum uric acid (26% vs. 4% - 15%) abnormalities, and hyperglycemia (28% vs. 8% - 16%) than other racial groups. Asian/Pacific Islanders had a higher incidence of lipase abnormalities (23% vs. 11% - 15%), total bilirubin (92% vs. 75% - 77%) and total cholesterol (62% vs. 39% - 53%) elevations than other racial groups.

9.2 Pediatric Program

Study AI424020 (PACTG 1020-A, 020)
A pediatric protocol designed to collect safety and pharmacokinetic data in infants greater than 3 months of age, children and adolescents is currently being conducted by the Pediatric AIDS Clinical Trials Group. This study is an open-label multicenter study of atazanavir as part of combination antiretroviral regimens in HIV-infected infants, children, and adolescents ages 3 months and 1 day to 21 years, who are either ART-naïve or ART-experienced.

At the time of submission of this NDA, 48 subjects had been enrolled and treated. Nineteen subjects discontinued treatment and twenty-nine are continuing to receive therapy. Dosing has not been determined yet for any of the protocol defined age groups due to wide variability in PK data.

There were two deaths of enrolled subjects reported during the study period. In the first report, a 14 year old female discontinued prematurely from the study due to worsening of HIV-related cardiomyopathy. Of note, this patient had several drug levels performed during the study; no study drug was detected in any sample. In October 2001 the patient started LPV/RTV, 3TC, d4T, and continued enalapril, digoxin and furosemide for her cardiac disease. According to the patients mother she was stable until January 2002 when she was hospitalized for candida esophagitis. On January 29, 2002 she was referred to the ER for decompensated CHF. She continued to deteriorate and developed full cardio-respiratory arrest and died on February 9, 2002.

The second patient was a 17 year old male who discontinued treatment at week 17 for mild asymptomatic first degree heart block. Per the study site the patient died at an outside hospital six months later, probably due to PCP pneumonia. He had been non-compliant with meds for at least six months at the time of his death and had CD4 counts < 50 for at least two years.

Eight subjects discontinued for adverse events: persistent emesis (2); increased bilirubin (2); pancreatitis (1); first degree heart block (2); and non-treatment related cardiomyopathy (1). The two events of persistent emesis, first degree AV block and increased bilirubin were believed to be related to treatment with atazanavir.

A 21 month old male receiving ATV/d4T/3TC was discontinued from treatment after approximately 5 months of therapy for elevations in total and direct bilirubin, GGT and transaminases. Lactic acid level at the time of study discontinuation was 2.5. An ultrasound performed for evaluation of elevated direct bilirubin was remarkable for gallstones and the patient received Actigel for two weeks prior to discontinuation from the study. All LFTs reportedly normalized one day following treatment interruption. The investigator judged the elevated bilirubin as possibly related to atazanavir, but more likely related to gallstones and the BMS physician judged the event possibly related to all of the study drugs.

A six year old G6PD deficient male who received 97 weeks of therapy with ATV/d4T/ddI was discontinued from the study for elevations of total/direct bilirubin, GGT, and transaminases. The subject had experienced an intercurrent viral illness at the time of treatment discontinuation and the investigator suggested that the elevated LFTs could be related to atazanavir therapy or increased hemolysis due to G6PD deficiency. The BMS physician judged the events as possibly related to study therapy.

The two subjects discontinuing for first degree heart block were asymptomatic and discontinued therapy at the discretion of the investigator.

The eleven discontinuations not related to adverse events were due to: lost-to-followup/compliance (3); protocol-defined treatment failures (7), and guardian decision to use protocol-disallowed medication (1).

A total of 22/48 (47%) of subjects reported any adverse event and 1/48 (2%) subjects reported grade 3-4 adverse events. Grade 3-4 lab abnormalities were reported in 22/48 (60 %) of subjects. Adverse events and grade 3-4 lab abnormalities are summarized in the following table:

Safety Results for All Treated Subjects		
Atazanavir and Dual NRTIs (N = 48)		
Deaths	2 (4%)	
Adverse events[a]: n (%)	**Grade 1 - 4**	**Grade 3 - 4**
Any adverse event	22 (46%)	
Vomiting	2 (4%)	--
Jaundice	1 (2%)	--
Icteric Sclera	3 (6%)	1 (2%)
Abnormal Fat Distribution	1 (2%)	--
Asymptomatic Prolongation of PR Interval	11 (23%)	--
Decrease in Heart Rate	7 (15%)	--
Prolongation of QTcB interval	2 (4%)	--
Prolongation of QT interval	2 (4%)	--
QRS Duration	1 (2%)	--
Grade 3 - 4 Lab Abnormalities[a]: n (%)		29 (60%)
Neutropenia		1 (2%)
Direct Bilirubin		1 (2%)
Indirect Bilirubin		18 (38%)
Total Bilirubin		16 (33%)
ALK Phosphatase		1 (2%)
AST (SGOT)		1 (2%)
GGT		1 (2%)
[a] Subjects may have had more than one adverse event reported.		

Serial ECG tracings were obtained on an elective basis at trough (24 hours post-prior dose) and during two post-dose windows (2 - 3 hours and 4 - 6 post-dose). Asymptomatic prolongation of the PR interval and other asymptomatic ECG abnormalities were the most common adverse events reported in this study.

Ten (45%) of the 22 subjects with available ECG data were reported to have an abnormality of some type. Seven (7) of the 10 subjects had first degree AV block; in general PR intervals in these subjects corresponded to borderline prolongation of PR interval beyond thresholds adjusted for age and do not appear to be clinically significant. In four subjects first degree AV Block was an isolated finding while in 3 subjects additional findings of sinus bradycardia (2 subjects) or other non-specific ST/T wave changes (1 subject) were also noted. The remaining 3 subjects reported sinus bradycardia (1 subject), an abnormal U wave (1 subject), and both supraventricular premature beats as well as non-specific ST/T wave changes (1 subject).

The QTcB intervals measured in this study decreased, on average, after administration of atazanavir. Although a slight increase was observed from 2 - 3 hours to 4 - 6 hours after dosing, the interval lengths observed at 4 - 6 hours were still shorter, on average, than those observed at the trough. No subjects had any ECG with QTcB intervals or ΔQTcB values defined as prolonged (i.e. no QTcB > 470 msec or ΔQTcB > 60 msec). Three subjects (all females) had QTcB intervals defined as borderline (QTcB in the range 451 - 470 msec) and two other subjects (one male, one female) had QTcB changes from trough defined as borderline (QTcB in the range 30 - 60 msec).

The Tmax in the pediatric population tended to occur between 2 and 6 hours after dosing. There was a mean increase in PR of 6.89 msec at 2 - 3 hours post dose relative to trough. No subject had any PR defined as prolonged for the age appropriate values and seven subjects had one or more tracings with borderline PR interval prolongation.

In summary, preliminary data from pediatric study 020 indicate that the adverse event profile of atazanavir is generally similar to that observed in adults. Further data need to be collected in order to define safe and effective doses for pediatric subjects.

9.3 Data Available or Needed in Other Populations

Renal Impairment

No studies were performed to examine the rate of elimination of atazanavir after administration to renally impaired patients. In addition it is unknown what percentage of the absorbed dose (as opposed to the administered dose) of atazanavir is renally excreted. As a result, no recommendations will be made in product labeling for dosing of atazanavir in patients with decreased creatinine clearance. However, as this drug is predominantly excreted through other pathways, it is not expected that renal impairment will significantly impact atazanavir exposures.

Hepatic Impairment
Reyataz® has been studied in adult patients with moderate to severe hepatic impairment (14 Child-Pugh Class B and 2 Class C subjects) after a single 400-mg dose. The mean AUC and mean half-life were 42% and 88% greater in patients with impaired hepatic function than in healthy subjects. On this basis, a dose of ATV 300 mg once-daily will be recommended for patients with moderate or severe hepatic impairment.

Pregnancy
Atazanavir has been assigned pregnancy category B. At maternal doses producing the systemic drug exposure levels equal to (in rabbits) or two times (in rats) those at the human clinical dose (400 mg/day), atazanavir did not produce teratogenic effects. At maternally toxic drug exposure levels two times those at the human clinical dose, atazanavir caused body weight loss or weight gain suppression in the offspring.

Hyperbilirubinemia occurred in most patients undergoing treatment with atazanavir. It is not known if administration to the mother during pregnancy will exacerbate physiological hyperbilirubinemia and lead to kernicterus in neonates and young infants.

There are no adequate and well-controlled studies of atazanavir in pregnant women. A number of women became pregnant while receiving atazanavir in clinical trials. In general, women who carried their pregnancies to term received atazanavir for 4-6 weeks while pregnant. When pregnancy was diagnosed, they were discontinued from study and received other medications as prescribed by their physicians for the remainder of the pregnancy. No maternal or fetal complications were reported in this group of women.

Two women enrolled in clinical trials of atazanavir became pregnant on study and received atazanavir for at least 36 weeks while pregnant; each woman delivered a healthy infant. One woman receiving atazanavir in combination with stavudine and didanosine developed a clinical syndrome consistent with lactic acidosis, as well as other medical problems, shortly following delivery. Atazanavir should be used in pregnancy only if the potential benefit justifies the potential risk.

Geriatrics
In a pharmacokinetic study of young versus elderly subjects, there were no clinically important pharmacokinetic differences observed due to age. In a safety analysis, age could not be evaluated because there were few subjects > 65 years of age in enrolled in clinical studies.

10 Conclusions, Recommendations, and Labeling

10.1 Conclusions Regarding Safety and Efficacy

In an intent-to-treat analyses, the percentage of patients achieving HIV viral load below limits of quantification at 48 weeks of treatment appeared to be similar between atazanavir as compared to efavirenz or nelfinavir in three studies of treatment-naïve subjects. In one treatment-experienced study of patients failing a PI-based regimen, atazanavir was inferior to lopinavir/ritonavir at 24 weeks; however, multiple analyses performed by FDA and the applicant indicated that atazanavir has activity in this population of patients. No differences in treatment effect were noted when data was analyzed by gender or race.

Use of atazanavir appeared to be well-tolerated with relatively few subjects discontinuing for treatment-related adverse events potentially attributable to atazanavir use. Discontinuations due to treatment-related adverse events were infrequent; they included hyperbilirubinemia/jaundice, abnormal liver enzyme tests, rash/allergic reaction, lipodystrophy, lactic acidosis syndrome and peripheral neuropathy. In general, each of these events led to discontinuation of fewer than 1-2% of subjects. Some of these adverse events are currently attributed to the NRTI background of antiretroviral therapy. Other uncommon but clinically important events leading to discontinuation of atazanavir-treated patients were hypertriglyceridemia, hyperglycemia, and cardiac conduction abnormalities.

Adverse events that were most commonly reported in all clinical trials across all treatment regimens included infection, nausea, vomiting, headache, diarrhea, and abdominal pain. Other adverse events included peripheral neurologic symptoms, fatigue, insomnia, and rash.

The adverse event profile of atazanavir appeared to be generally similar to that of comparators with a few exceptions. Jaundice and/or scleral icterus were reported in 15-24% of patients receiving atazanavir; these events were uncommon in comparators. The clinically important safety issues of hyperbilirubinemia, PR interval prolongation, and drug-drug interactions appear to be well-characterized.

Atazanavir has the potential treatment benefits of once daily dosing with a low "pill burden" and a minimal impact on lipid profiles. The favorable lipid profiles observed in atazanavir-treated patients may allow some patients to avoid the use of lipid-lowering agents, and as a result, the additional pill burden, adverse events, and potential drug-drug interactions associated with this class of medications. Long term benefits of the lower lipid profiles observed in HIV-infected patients taking atazanavir remain to be clarified.

Post-marketing commitments include monitoring of long-term safety and efficacy in treatment-naïve patients and long-term safety of treatment-experienced patients, evaluation of a ritonaivr-boosted dose of atazanavir in treatment-naive patients, further

characterization of clinically important drug-drug interactions, and further characteriztion of clinical outcomes of patients failing atazanavir-based regimens.

10.2 Recommendations on Approvability

Based on review of the data submitted by Bristol-Myers Squibb in support of NDA 21-567, it is recommended that this application for atazanavir sulfate for once daily administration to HIV-infected patients as a component of "highly active antiretroviral therapy" (HAART) be approved.

30 page(s) of revised draft labeling has been redacted from this portion of the review.

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/s/

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